Longitudinal Changes in Tear Evaporation Rates After Eyelid Warming Therapies in Meibomian Gland Dysfunction

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Purpose. Lid warming is the major treatment for meibomian gland dysfunction (MGD). The purpose of the study was to determine the longitudinal changes of tear evaporation after lid warming in patients with MGD.

Methods. Ninety patients with MGD were enrolled from a dry eye clinic at Singapore National Eye Center in an interventional trial. Participants were treated with hot towel ($n = 22$), EyeGiene ($n = 22$), or Blephasteam ($n = 22$) twice daily or a single 12-minute session of Lipiflow ($n = 24$). Ocular surface infrared thermography was performed at baseline and 4 and 12 weeks after the treatment, and image features were extracted from the captured images.

Results. The baseline of conjunctival tear evaporation (TE) rate ($n = 90$) was 66.1 ± 21.1 W/min. The rates were not significantly different between sexes, ages, symptom severities, tear breakup times, Schirmer test, corneal fluorescein staining, or treatment groups. Using a general linear model (repeat measures), the conjunctival TE rate was reduced with time after treatment. A higher baseline evaporation rate (≥66 W/min) was associated with greater reduction of evaporation rate after treatment. Seven of 10 thermography features at baseline were predictive of reduction in irritative symptoms after treatment.

Conclusions. Conjunctival TE rates can be effectively reduced by lid warming treatment in some MGD patients. Individual baseline thermography image features can be predictive of the response to lid warming therapy. For patients that do not have excessive TE, additional therapy, for example, anti-inflammatory therapy, may be required. (ClinicalTrials.gov number, NCT01683318 and NCT01448369.)

Keywords: tear evaporation, clinical study, randomized controlled trial, meibomian gland dysfunction, dry eye, human, longitudinal study

Meibomian gland dysfunction (MGD) is defined as "a chronic diffuse abnormality of the meibomian glands commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion."[1] This may lead to an imbalance of tear film composition leading to signs and symptoms of ocular inflammation and ocular surface disease.[2]

In MGD, pathologic alterations in the compositions of the meibomian gland secretions result in the thickening of the meibum, subsequently leading to the blockage of the glandular ducts. The occlusion may also be attributed to excessive colonization by bacterial commensals and exfoliated skin materials and crusts as a result of hyperkeratinization of the glandular ducts. These aberrations cumulatively result in a hyposecretion of lipids into the tear reservoir at the lid margins.[3] The lipid abnormalities lead to reduced tear film stability, loss of lubrication, and damage to the corneal epithelium due to excessive evaporation and the resultant desiccation. As the disease progresses, these pathophysiologic alterations eventually lead to the emergence of disease symptoms including ocular discomfort and afflicted visual quality.[4]

Warming the eyelid represents one of the earliest and the most commonly prescribed therapy for MGD. The primary therapeutic effect lies in easing the flow of meibum and reducing glandular obstruction. It is expected that raising the eyelid temperature would lead to conformational changes in the lipid hydrocarbon chains (i.e., *trans* to *gauche* rotomers) in the meibum, thus increasing the disorder in the packing of these lipids and enhancing delivery and secretion out of the glandular ducts.[5,6] Eyelid warming also serves as adjunct to additional treatment such as oral (systemic) and topical antibiotics, manual expression of glands, artificial tears, and steroid ointments.[3,7] Effectively, tear evaporation (TE) should be retarded if the treatment achieved its goal. This group recently reported on a noninvasive technique to measure TE using thermography[8]; this was then applied to subsequent intervention trials.

Recently clinical trials were completed to evaluate the effectiveness of eyelid warming devices with traditional method

Table 1. Baseline TE Levels of Participants

Clinical Characteristics	Total		Towel		EyeGiene		Blephasteam		Lipiflow		
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*P* Value
All	90	66.1 (21.1)	22	67.0 (21.7)	22	57.7 (22.7)	22	69.7 (22.6)	24	70.0 (16.0)	0.18
Sex											
Male	28	59.8 (20.8)	5	59.9 (26.9)	7	57.9 (26.4)	9	53.9 (16.8)	7	69.2 (15.1)	0.56
Female	62	68.9 (20.8)	17	69.0 (20.4)	15	57.6 (21.8)	13	80.6 (19.8)	17	69.9 (16.9)	**0.03**†
P value		0.057		0.42		0.97		**0.004***		0.93	
Age											
≤55	45	66.5 (20.6)	9	64.8 (19.3)	12	63.8 (22.9)	14	70.4 (24.1)	10	65.8 (14.8)	0.87
>55	45	65.6 (21.8)	13	68.5 (23.9)	10	50.3 (21.3)	8	68.5 (21.2)	14	72.4 (16.9)	0.08
P value		0.85		0.71		0.17		0.86		0.33	
Irritation											
≤50.2	56	65.9 (19.3)	10	66.5 (12.2)	17	63.4 (22.4)	16	68.1 (22.7)	13	66.2 (16.2)	0.92
>50.2	34	66.3 (24.1)	12	67.4 (27.9)	5	38.2 (9.9)	6	73.8 (24.0)	11	73.7 (15.7)	**0.029**‡
P value		0.94		0.92		**0.002***		0.61		0.26	
Tear breakup time											
TBUT ≤2 s	40	64.0 (20.1)	12	63.4 (20.2)	6	50.5 (15.0)	13	70.3 (23.8)	9	64.7 (15.0)	0.27
TBUT >2 s	50	67.7 (21.9)	10	71.2 (23.7)	16	60.4 (24.9)	9	68.8 (22.1)	15	72.7 (16.4)	0.43
P value		0.41		0.42		0.38		0.89		0.25	
Schirmer's I test											
≤8 mm	45	68.7 (20.5)	8	73.6 (21.5)	11	57.3 (18.5)	12	73.8 (21.9)	14	70.6 (18.9)	0.20
>8 mm	45	63.4 (21.5)	14	63.1 (21.6)	11	58.0 (27.3)	10	64.7 (23.6)	10	68.4 (11.8)	0.75
P value		0.23		0.29		0.94		0.36		0.75	
Corneal staining											
Superior											
≤1	81	65.7 (21.3)	18	66.0 (21.8)	19	55.7 (23.6)	20	70.3 (22.6)	24	69.7 (16.0)	0.11
>1	9	69.1 (19.6)	4	71.4 (23.6)	3	70.0 (13.2)	2	63.3 (19.6)	0	0	0.91
P value		0.65		0.66		0.33		0.69		–	
Inferior											
≤1	61	65.9 (21.8)	12	70.2 (21.5)	14	50.9 (20.5)	16	70.2 (25.02)	19	70.5 (15.8)	**0.031**§
>1	29	66.5 (19.9)	10	63.0 (22.4)	8	69.5 (22.8)	6	68.1 (16.2)	5	66.5 (18.5)	0.92
P value		0.90		0.45		0.064		0.85		0.63	
Nasal											
≤1	78	65.5 (21.2)	18	68.5 (23.0)	17	53.3 (19.6)	20	69.0 (23.5)	23	69.0 (16.1)	0.063
>1	12	69.9 (21.0)	4	59.9 (15.1)	5	72.5 (28.8)	2	75.86 (11.1)	1	85.1	0.71
P value		0.50		0.49		0.098		0.70		0.34	
Temporal											
≤1	79	66.4 (20.8)	19	71.0 (20.3)	16	52.7 (20.2)	20	69.0 (23.5)	24	69.7 (16.0)	**0.029**§
>1	11	63.8 (23.4)	3	41.4 (9.5)	6	71.0 (25.6)	2	75.9 (23.8)	0	0	0.16
P value		0.71		**0.024***		0.092		0.70		–	
Central											
≤1	77	66.8 (20.9)	17	72.2 (20.8)	18	54.7 (19.9)	19	68.9 (24.2)	23	70.5 (15.9)	**0.041**§
>1	13	61.7 (22.5)	5	49.1 (15.2)	4	70.9 (33.0)	3	74.3 (8.3)	1	50.4	0.36
P value		0.42		**0.033***		0.21		0.49		0.23	

Bold indicates significance.

* $P < 0.05$.

† Post hoc Bonferroni test shows that, in the female group, Blephasteam > EyeGiene ($P = 0.019$).

‡ Post hoc Bonferroni test shows that Lipiflow > EyeGiene in the more symptomatic group ($P = 0.031$).

§ Post hoc Bonferroni test shows no significant difference between treatments.

of using a warm towel for the treatment of MGD via objective clinical scoring, assessment of ocular surface parameters, documentation of meibography, measurement of TE, and changes in tear lipid profiles in an Asian population. The clinical efficacy has been published separately.[9] The clinical efficacy of Lipiflow, a form of thermopulsation treatment compared with warm towel, was also examined.[10] However, none of these reports have included the effect of lid warming on TE rates. The aim of the current report is to establish the longitudinal effects of eyelid warming on TE rates with eyelid warming treatment over 12 weeks of treatment period. The possible effect of baseline demographic and clinical parameters on TE will also be studied. Another aim is to explore the features extracted from the TE thermography and compare the predictive outcome of reduced irritation and conjunctival TE rate after 12 weeks of treatment.

Methods

Study Design and Participants

The use of eyelid warming devices in these parallel treatment groups, EyeGiene (Eyedetec Medical, Inc., Danville, CA, USA), Lipiflow (TearScience, Morriville, NC, USA), and Blephasteam (Laboratoires Thea, Clermont-Ferrand, France), and warm towel compress in participants with MGD have been described previously.[9,10] The SingHealth Centralized Institutional Review Board has approved this study, and the Tenets of the

Table 2. Evaporation Rates at Three Different Time Points

Evaporation Rate, W/min	Total, $n = 90$	Towel, $n = 22$	Eyegiene, $n = 22$	Blephasteam, $n = 22$	Lipiflow, $n = 24$	P Value
Baseline						
Mean (SD)	66.1 (21.1)	67.0 (21.7)	57.7 (22.7)	69.7 (22.6)	69.7 (16.0)	
Median (range)	69.1 (78.8)	71.5 (74.38)	51.3 (77.5)	69.6 (66.1)	72.3 (57.5)	0.18
Week 4						
Mean (SD)	64.3 (22.7)	71.2 (21.8)	61.9 (22.6)	67.9 (24.3)	56.8 (20.8)	
Median (range)	62.5 (85.5)	66.2 (63.3)	56.1 (66.5)	74.5 (69.4)	56.7 (85.5)	0.14
Week 12						
Mean (SD)	60.5 (19.9)	63.6 (22.1)	61.5 (18.1)	63.5 (22.4)	53.8 (16.5)	
Median (range)	54.8 (94.5)	57.0 (73.8)	56.5 (72.8)	55.5 (89.2)	52.6 (59.8)	0.29
P value	0.045*†	0.61	0.48	0.46	0.002*‡	

* $P < 0.05$.
† Post hoc test: all comparisons, $P > 0.05$.
‡ Post hoc test: week 4 < baseline ($P = 0.046$) and week 12 < baseline ($P = 0.009$).

Declaration of Helsinki were followed. From February 2012 to March 2013, all patients who met the eligibility criteria at the dry eye clinic in Singapore National Eye Center went through study briefing and were invited for screening. Written informed consent was obtained from the enrolled participants by the clinical trial coordinator. The study was registered at the Clinicaltrials.gov database (NCT01683318 and NCT01448369).

All participants were allowed to use eye lubricants. The use of steroids, antibiotics, and anti-inflammatory eye drops such as Restasis were not allowed as specified under the inclusion criteria. The following clinical parameter were measured: the change in the clinical irritation scores, the tear breakup time (TBUT), Schirmer's I test, the change in corneal fluorescein staining, and the number of plugged meibomian gland openings after 3 months of treatment from baseline values. Patients' irritation symptoms were recorded using the Symptom Assessment iN Dry Eye (SANDE) questionnaire as previously described.[11] The evaluators were masked to the treatment modality.

The following inclusion criteria for this study have been published,[9] and for easy reference are specified here: at least one of eight dry eye symptoms experienced often or all the time; at least one meibomian gland opening with pouting and a visible plug above the eyelid margin that cannot be removed by gentle wiping with a cotton tip; and no ocular pathology requiring treatment within the last month and during the study.[9]

Tear Evaporation Rates

Ocular thermography was performed at baseline and 4 and 12 weeks after treatment. A sequence of thermographic images was captured over 20 seconds for each eye with the patient's head resting on the chin rest in front of the infrared thermography camera (VarioTHERM headII; InfraTec, Dresden, Germany). The TE rates were calculated using the first law of thermodynamics from the thermography data as previously described.[8,12,13] The evaporimetry values calculated based on temperature changes would also be associated with and indicative of dynamic changes of the tear morphology due to tear spreading between blinks and should not be interpreted to be merely a function of physical evaporation of tears from a uniformly thick tear profile. However, the term "tear evaporation" will be used throughout this manuscript for simplicity. The thermography was performed before the other tests (TBUT, Schirmer's I test, number of plugged glands, corneal

Table 3. Multivariate Models (Logistic Regression) With the Evaporation Rate at Different Times as the Dependent Variable, Relative to the Reference Category

Covariate	Crude OR (95% CI)*	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡	Adjusted OR (95% CI)§
Time after treatment				
Baseline	1.0	1.0	1.0	1.0
Week 4	0.788 (0.430–1.444)	0.771 (0.409–1.452)	0.769 (0.406–1.453)	0.730 (0.364–1.466)
Week 12	0.414 (0.222–0.773)¶	0.383 (0.199–0.736)¶	0.379 (0.196–0.732)¶	0.319 (0.155–0.656)¶
Treatment type				
Warm towel	–	1.0	1.0	1.0
EyeGiene		0.136 (0.045–0.406)¶	0.117 (0.038–0.359)¶	0.403 (0.113–1.434)
Blephasteam		0.081 (0.026–0.249)¶	0.074 (0.024–0.232)¶	0.297 (0.079–1.123)
Lipiflow		0.129 (0.043–0.392)¶	0.122 (0.040–0.375)¶	0.417 (0.116–1.496)
Sex				
Male	–	–	1.0	1.0
Female			0.612 (0.339–1.103)	0.936 (0.486–1.803)
Baseline evaporation				
<66 W/min	–	–	–	1.0
≥66 W/min				0.145 (0.076–0.279)¶

* Independent variable (covariate) is time after treatment. A lower odds ratio than 1 indicates less likelihood of having a higher conjunctival evaporation rate than 66 W/min, compared to the reference category.
† In this model, covariates include time after treatment and treatment type.
‡ In this model, covariates include time after treatment, sex, and treatment type.
§ In this model, covariates include time after treatment, sex, and baseline evaporation rate.
¶ $P < 0.05$.

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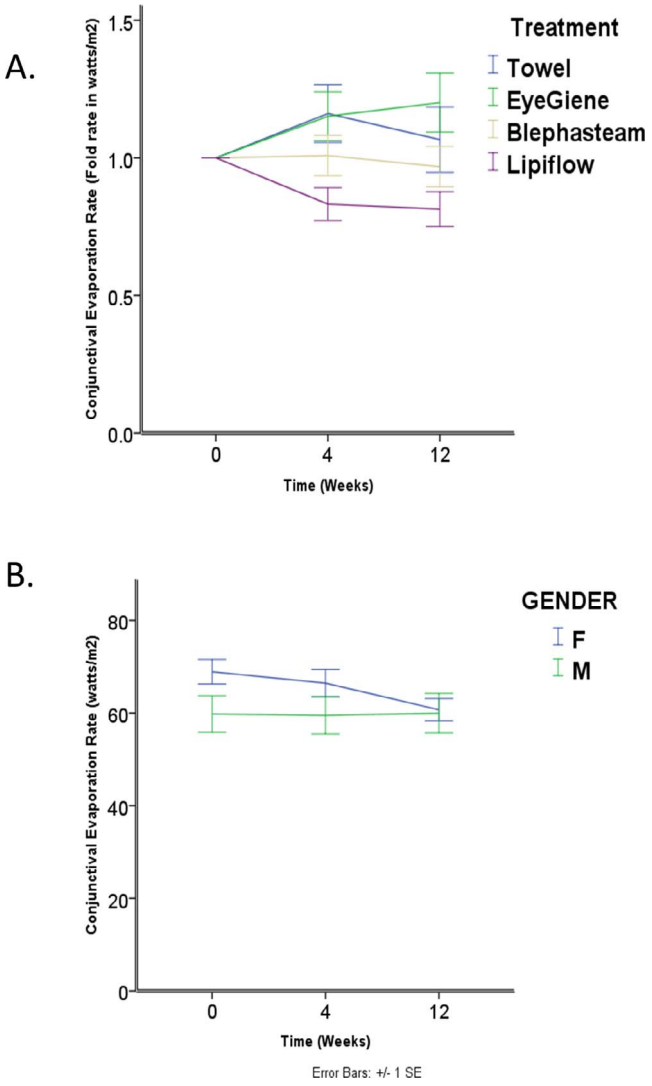

Figure 1. The plot shows the mean (±1 SE) of TE (**A**) in the four treatment groups with time. (**B**) Stratified by sex.

fluorescein staining). Where tear lipid thickness was performed, it was done before the TBUT but after thermography.[10]

Data Acquisition and Preprocessing

The ocular thermography was performed after 3 months of treatment from week 0. The patients who responded and not responded to the treatment were grouped based on the clinical parameters measured. The ocular thermography images of these two groups of patients were obtained for further analysis. The first 20 images after the first blink were taken and were preprocessed using a self-developed algorithm with manually delineated ocular region.[8]

Features

Features were extracted from the ocular thermography. In this work, texture methods[14–17] were used to extract the following features. One feature was obtained using Fourier Spectrum (FS), one with fractal dimension (FD), and a few others using the Gray Level Co-Occurrence matrix.

Fourier Spectrum. The periodicity of an image texture can be inferred directly from its Fourier power spectrum.[18] This feature analyses the textured images by decomposing the image into its frequency and orientation components.[19] In this work, the AC power of the image is used as a texture descriptor.

Fractal Dimension. An FD is a number that describes how an object fills its space quantitatively. It is useful in modeling an object having a statistical quality of roughness and self-similarity at different scales.[18] In this work, the sequential box counting algorithm was used for FD estimation for a given image.[20] An estimate of FD obtained was used as a texture descriptor.

Gray Level Co-Occurrence Matrix. This method was used to calculate the second-order statistical texture features from the images.[21] The variations of texture are evaluated using a gray-tone spatial dependence matrix where the pixels are separated with a specified distance. The autocorrelation, maximum probability, dissimilarity, entropy, cluster shade, sum average, sum entropy, and sum variance were computed using this method. The autocorrelation feature is used to assess the amount of regularity and the fineness of the texture present in the image, whereas entropy is the measure of randomness.

Table 4. Using Individual Baseline Image Feature to Predict Change in Irritation Experienced at Week 12 From Baseline

Texture Extraction	No Response, $n = 40$	Response, $n = 41$	*P* Value
Dftenergy	0.45 (0.19)	0.56 (0.26)	0.034*
Fractal	0.9997 (0.00013)	0.9998 (0.00016)	0.045*
Autocorrelation	0.49 (0.18)	0.60 (0.23)	0.03*
Maxprobability	0.84 (0.14)	0.81 (0.15)	0.40
Dissimilarity	0.59 (0.17)	0.69 (0.20)	0.023*
Entropy	0.67 (0.13)	0.70 (0.14)	0.43
Clustershade	0.72 (0.24)	0.58 (0.31)	0.023*
Sumaverage	0.71 (0.12)	0.77 (0.15)	0.042*
Sumentropy	0.69 (0.13)	0.71 (0.14)	0.44
Sumvariance	0.47 (0.21)	0.58 (0.26)	0.034*

* $P < 0.05$.

Statistical Analyses

Data were checked for normality with the skewness and kurtosis test to determine the appropriate parametric or nonparametric test. To test for differences among groups for baseline characteristics and the various outcomes, the relevant χ^2 test, 1-way ANOVA, and Kruskal-Wallis equality-of-populations rank test were used. Bonferroni was used in the post hoc testing after ANOVA for baseline results. Where there was difference among groups, the relevant Student's *t*-test or Wilcoxon rank sum test to determine the source of difference was performed. Multivariate analysis was first performed with logistic regression to examine the factors that would decrease the evaporation rate from above 66 W/min to below that (mean baseline). A second analysis was performed using the SPSS linear mixed model procedure. A statistically significant difference was based on the $\alpha = 0.05$ level. Post hoc testing was not done for comparisons of image analysis parameters between response and nonresponse subgroups. However, because there were 10 such comparisons, the level of significance may need to be 0.05/10 or 0.005 to account for multiple testing.

Results

Participants

Ninety patients with MGD participated in this study. The mean age of this cohort was 54.3 years (SD, 1.5 years; range, 22–81 years), with 69% being female. Fifty percent of patients had

Table 5. Multivariate Analysis Using Individual Baseline Image Feature to Predict Change in Irritation Experienced at Week 12 From Baseline

	Odds Ratio (95% CI)		
Texture Extraction	**Crude**	**Adjusted OR***	**Adjusted OR†**
Dftenergy	2.12 (0.87–5.14)	2.12 (0.87–5.15)	2.62 (1.02–6.75)‡
Fractal	2.60 (1.06–6.37)‡	2.67 (1.08–6.59)‡	3.07 (1.19–7.95)‡
Autocorrelation	10.40 (1.20–90.33)‡	10.91 (1.24–96.25)‡	22.56 (2.11–240.79)‡
Maxprobability	0.27 (0.014–5.42)	0.23 (0.011–4.96)	0.21 (0.009–4.70)
Dissimilarity	16.21 (1.39–188.85)‡	19.59 (1.57–244.43)‡	32.25 (2.31–450.59)‡
Entropy	3.90 (0.14–107.41)	4.93 (0.16–153.61)	5.48 (0.16–182.64)
Clustershade	0.15 (0.028–0.81)‡	0.15 (0.027–0.80)‡	0.079 (0.012–0.508)‡
Sumaverage	32.11 (1.09–946.35)‡	34.87 (1.15–1055.05)‡	101.44 (2.53–4072.79)‡
Sumentropy	3.72 (0.14–100.89)	4.74 (0.15–147.06)	5.32 (0.16–176.05)
Sumvariance	7.97 (1.13–56.11)‡	8.20 (1.15–58.29)‡	15.98 (1.88–135.91)‡

* Age and sex adjusted.
† Age, sex, and treatment adjusted.
‡ $P < 0.05$.

some component of aqueous deficiency dry eye (Schirmer's I of 8 mm or less at 5 minutes), whereas 44% had severe evaporative tendency or very unstable tear film (TBUT of less than 2 seconds). Twenty-two patients had a hot towel treatment, 22 used EyeGiene, and 22 were treated with Blephasteam. Finally, 24 patients had one single session of Lipiflow treatment. The treatment outcomes for participants in the trial have been published.[9,10] The comparison of the efficacy of these treatment groups has been presented elsewhere. Briefly, the discomfort significantly improved after 3 months, but the TBUT, Schirmers, and corneal staining did not.

Baseline TE Levels

The evaporation rate was weakly correlated to tear lipid thickness at baseline in the Lipiflow group, the only patients with lipid thickness measurements ($r = -0.292$). The average baseline conjunctival TE rate ($n = 90$) was 66.1 W/min (SD, 21.1). With two exceptions, the rates were not significantly different (Table 1) between sexes, ages, different symptom severities, TBUT, Schirmer's test, corneal fluorescein staining, or between treatment groups. On Bonferroni post hoc testing, the female participants had a greater evaporation rate at baseline compared with the male participants in the Blephasteam group ($P = 0.004$), and the Lipiflow group had more patients with greater irritation than the EyeGiene group ($P = 0.031$). The baseline TE rates were not associated with a change in Schirmers and TBUT after treatment (data not shown). When the age and categories of symptoms were explored as continuous variables, similar conclusions from above were obtained (data not shown).

Analysis of the Change in Evaporation

The evaporation rates at three time points of the study are summarized in Table 2. The reduction in evaporation rate was significant only in the Lipiflow group ($P = 0.002$) and for all patients overall ($P = 0.045$).

In regression models, evaporation rate was significantly reduced at week 12 compared with baseline (Table 3, first

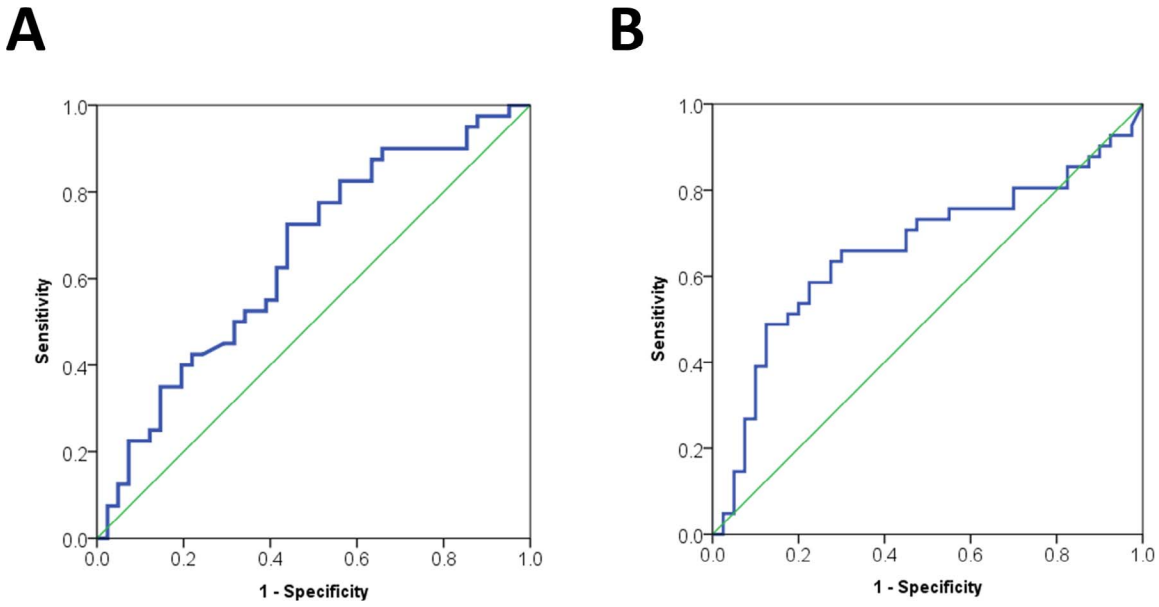

Figure 2. (**A**) Receiver operating curves using the baseline feature clustershade and (**B**) dissimilarity. A lower level of clustershade predicts symptomatic response to lid warming treatment, whereas a higher level of dissimilarity predicts such a response (see text for area under curve values).

Table 6. Using Individual Baseline Image Feature to Predict Change in Conjunctiva Evaporation Rate Experienced at Week 12 From Baseline

Texture Extraction	No Response, $n = 40$	Response, $n = 41$	*P* Value
Dftenergy	0.63 (0.23)	0.39 (0.17)	<0.001*
Fractal	0.99980 (0.0013)	0.99966 (0.00012)	<0.001*
autocorrelation	0.65 (0.22)	0.44 (0.15)	<0.001*
maxprobability	0.79 (0.15)	0.86 (0.14)	0.058
Dissimilarity	0.73 (0.18)	0.55 (0.16)	<0.001*
Entropy	0.72 (0.13)	0.66 (0.13)	0.034
Clustershade	0.51 (0.31)	0.79 (0.17)	<0.001*
Sumaverage	0.81 (0.13)	0.67 (0.10)	<0.001*
Sumentropy	0.73 (0.13)	0.67 (0.13)	0.027
Sumvariance	0.65 (0.25)	0.41 (0.16)	<0.001*

* $P < 0.05$.

row). All three treatment modalities (EyeGiene, Blephasteam, and Lipiflow) were significantly more effective than a warm towel in reducing TE (Table 3, second row), but when evaporation rates were adjusted for differences in baseline evaporation, these effects were no longer significant. However, when baseline evaporation was adjusted for, there was a trend for the Lipiflow group showing a greater reduction of TE after treatment (Fig. 1A).

Women had a trend for greater reduction in TE (Fig. 1B); however, this sex effect was not significant when introduced as a covariate (Table 3, third row). The borderline sex effect was attributed to differences in baseline evaporation rates; females have a borderline higher baseline evaporation rate (Table 1; $P = 0.057$). A higher baseline evaporation rate was a significant predictor of reduction in evaporation rate after treatment (Table 3, last row).

Baseline TBUT or Schirmer values were not associated with change in evaporation rates after treatment ($P = 0.62$ and $P = 0.52$, respectively). However, the change in conjunctival evaporation rates was weakly correlated to change in TBUT after treatment ($r = 0.21$, $P = 0.047$).

Baseline Thermography Characteristics Predictive of Change in Irritation

Seven of 10 features were significant predictors of the change in irritation after treatment (Table 4). On multivariate analysis, higher values of the features dftenergy, fractal, autocorrelation, dissimilarity, sumaverage, and sumvariance were associated with reduced irritation level after treatment (Table 5). In contrast, lower values of the clustershade feature predicted symptomatic response after treatment.

Next, the receiver operating characteristics were shown using the clustershade (Fig. 2A) and dissimilarity (Fig. 2B) to predict symptomatic response. The best compromise of sensitivity and specificity for the prediction of symptomatic response using clustershade (threshold of 0.679) was 72.5% and 56.1%, respectively (area under the curve, 0.649; 95% confidence interval [CI], 0.530–0.769). On the other hand, the best compromise of sensitivity and specificity using dissimilarity (threshold 0.612) was 73.2% and 52.5%, respectively (area under the curve, 0.660; 95% CI, 0.537–0.783).

Baseline Thermography Characteristics Predictive of Change in Conjunctiva Evaporation Rate

Because baseline conjunctival evaporation could possibly predict evaporative response after treatment, the authors were interested to know if thermographic features at baseline can predict for evaporative response after treatment better than baseline evaporation. Although 7 of 10 features were associated with a decrease in conjunctival TE rates (Table 6), none of the odds ratios (Table 7) were more remarkable than baseline evaporation (Table 3).

Discussion

In this study, a statistically significant reduction of evaporation rate was detected in patients who had Lipiflow treatment compared with baseline (Table 2), and on multivariate analysis, the reduction of evaporation rate was significantly better in Eyegiene, Blephasteam, and Lipiflow treatments compared with a warm towel (Table 3). Furthermore, this study found that a higher baseline evaporation rate, but not TBUT or Schirmer value, was predictive of a decrease in TE rate after lid warming treatment in general (Table 3). Last, it was discovered that specific individual thermographic features at baseline were associated with symptomatic change after the lid warming treatment (Table 4).

This is the first study that measured TE rate up to 3 months after lid warming treatment. Ocular temperatures before and after Blephasteam treatment up to 5 minutes have been published previously, but these measurements were not calculated for TE rates.[22] No previous studies have measured

Table 7. Multivariate Analysis Using Individual Baseline Image Feature to Predict Change in Conjunctiva Evaporation Rate Experienced at Week 12 From Baseline

	Odds Ratio (95% CI)		
Texture Extraction	Crude	Adjusted OR*	Adjusted OR†
Dftenergy	0.224 (0.088–0.568)‡	0.215 (0.083–0.556)‡	0.217 (0.083–0.569)‡
Fractal	0.28 (0.11–0.70)‡	0.25 (0.095–0.64)‡	0.25 (0.096–0.65)‡
autocorrelation	0.25 (0.094–0.63)‡	0.24 (0.095–0.62)‡	0.25 (0.094–0.64)‡
maxprobability	2.60 (1.06–6.38)‡	3.66 (1.36–9.82)‡	3.63 (1.35–9.78)‡
Dissimilarity	0.16 (0.06–0.41)‡	0.13 (0.045–0.36)‡	0.12 (0.043–0.35)‡
Entropy	0.35 (0.14–0.85)‡	0.23 (0.083–0.63)‡	0.23 (0.083–0.64)‡
Clustershade	3.58 (1.43–8.95)‡	3.67 (1.45–9.30)‡	3.62 (1.41–9.33)‡
Sumaverage	0.22 (0.088–0.57)‡	0.22 (0.083–0.56)‡	0.22 (0.083–0.57)‡
Sumentropy	0.35 (0.14–0.85)‡	0.25 (0.091–0.67)‡	0.25 (0.09–0.67)‡
Sumvariance	0.22 (0.088–0.57)‡	0.22 (0.086–0.57)‡	0.22 (0.086–0.58)‡

* Age and sex adjusted.
† Age, sex, and treatment adjusted.
‡ $P < 0.05$.

TE after MGD treatment. The current results suggest that any method that is convenient and consistently delivering the right temperature may be more effective than a warm towel when targeting evaporation rates. The hot towel cools very quickly and therefore is inconvenient or may not achieve the required therapeutic effects.

Irritative symptoms in MGD patients were previously found to improve after lid warming.[9] The current findings suggest that these symptomatic improvements in this original publication were not due to purely subjective effects but could be related to reduced rates of TE. Previously, the association of changes in levels of specific tear lipids with TE rates was also reported,[23] and these lipids may have functional roles in stabilizing the tear. The reduction in evaporation rates in this paper could be due to the increased lipids delivered from the meibomian glands after eyelid warming. Eyelid warming alters the viscosity of meibum and de-occludes the ducts/orifices of meibomian glands. An increase in tear lipids or improvement in the composition of certain lipids would increase the barrier for tear evaporation of the aqueous tear or stability of the entire tearfilm,[23–27] as well as facilitate dynamic tear spreading between eyelid blinks.[28] In a previous paper, the patients who had symptomatic improvement also had an associated decrease in inflammatory lipids such as lysophospholipids.[23] Lid warming may have reduced retention time of lipids in the glands, thereby reducing generation of certain inflammatory lipids due to bacterial lipases or other enzymes.

The strengths of this study are uniform measurement of clinical parameters, clearly defined recruitment criteria, and inclusion of novel parameters like thermography. One limitation of the study is that the expressibility of the meibomian gland using a fixed force evaluator was not examined, nor was the consistency of the lipids documented. A further limitation of this study is that combinations of different baseline thermographic features to examine their receiver operating characteristics were not computed. It is possible that certain combinations of characteristics may predict symptomatic response to lid warming even better than one characteristic. Future studies will correlate inflammatory markers like tear cytokines with the TE rates and the association of levels of inflammatory lipids like prostaglandins or eicosanoids with TE rates.

In clinical practice, baseline TE may be used for suitability assessment prior to lid warming, as this study show that high baseline evaporation tends to have a reduction in TE rate. This might indicate that a patient with a higher evaporation rate before treatment is more likely to benefit and have a better prognosis (Table 4). On the other hand, patients with low TE at baseline may need other therapies such as anti-inflammatory or tear stabilizing formulations in addition to lid warming. Lipiflow may be more effective than other methods for reducing TE; however, it may be preferred if other factors such as cost can be mitigated, despite it being a more convenient treatment.

In conclusion, lid warming treatment is an effective way to reduce conjunctival TE in some patients. Alternative or additional anti-inflammatory therapy for MGD may be required for patients who presented with a relatively normal TE rate. Higher baseline evaporation rate was predictive of a decrease in TE rate after lid warming treatment.

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